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Effect of a Probiotic Preparation (VSL#3) on Cardiovascular Risk Parameters in Critically-Ill Patients

Sarvin Sanaie[1], Mehrangiz Ebrahimi-Mameghani[2*], Ata Mahmoodpoor[3], Kamran Shadvar[3], Samad EJ Golzari[4,5]

[1]*Student Research Center, Faculty of Nutrition, Tabriz University of Medical Sciences, Tabriz, Iran*
[2]*Nutrition Research Center, Faculty of Nutrition, Tabriz University of Medical Sciences, Tabriz, Iran*
[3]*Anesthesiology and Intensive Care Department, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran*
[4]*Cardiovascular Research Center, Tabriz University of Medical Sciences, Tabriz, Iran*
[5]*Students' Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran*

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ABSTRACT

Introduction: Cardiovascular disease (CVD) counts for a major portion of morbidity and mortality globally mostly accompanied by lipid abnormalities. Being at increased risk of cardiac injury, critically ill patients suffer from various lipid disorders. Lipid homeostasis has been efficiently restored by the introduction of probiotics. The aim of this trial was to determine the effect of probiotics on inflammation, antioxidant capacity and lipid peroxidation in critically ill patients.
Methods: Forty patients admitted to the intensive care unit were randomized to receive placebo or probiotic for 7 days. Serum levels of triglyceride (TG), total cholesterol, HDL-C, LDL-C and high- sensitivity C-reactive protein (hs-CRP) were measured before initiation of the study and on the 7th day.
Results: There was a significant difference between two groups regarding the levels of TG, HDL and hs-CRP at the end of the study (P= 0.043, <0.001 and 0.003, respectively); however, there was not a significant difference in total cholesterol and LDL-C levels.
Conclusion: Administration of probiotics in critically ill patients reduced the levels of TG and hs-CRP and increased HDL-C levels. However, no significant change was detected in levels of total cholesterol or LDL-C.

Introduction

Cardiovascular disease (CVD) counts for a major portion of morbidity and mortality globally mostly accompanied by lipid abnormalities.[1] Abnormal levels of high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C) and triglyceride (TG) could accompany a higher prevalence of CVD.[2] Elevated LDL-C and reduced HDL-C levels are already-confirmed CVD risk factors with evidence suggesting that significant increase in HDL-C could be set as an important therapeutic goal.[3] While critically ill patients frequently suffer from metabolic disturbances such as various lipid disorders, elevated triglyceride levels followed by increase in very low-density lipoprotein (VLDL), and low circulating HDL-C are their main characteristic in critically ill patients. LDL-C levels are also decreased.[4,5] Commonly seen in critically ill patients, systemic inflammation and sepsis also accompany severe metabolic imbalances including decreases in HDL-C and LDL-C and high levels of TG.[6-9] Association between systemic inflammation and lipid metabolism has been clearly established in many studies.[10] In sepsis, enhanced production of hepatic VLDL and/or inhibited peripheral and hepatic VLDL clearance lead to increase in plasma TG within VLDL. In contrast, sepsis decreases plasma cholesterol within LDL-C and mainly HDL-C.[11] Furthermore, lipid metabolism disorders are accompanied by worse prognosis in critically ill patients.[12] Indices of lipid metabolism have been found to be related to the severity of illness, the occurrence of sepsis and survival in critically ill patients.[13] In addition, ICU patients are at increased risk of cardiac disorders due to the underlying presence of coronary circulation atherosclerosis and other non-cardiac factors including increased tissue oxygen demands, anemia, sepsis, mechanical ventilation, and hemodynamic instability. Furthermore, assessment of myocardial injury as an independent determinant of hospital mortality would make it possible to recognize ICU patients at augmented risk of death.[14]
The incidence of myocardial injury is usually defined by elevated levels of cardiac troponin I.15 Levels

***Corresponding author:** Mehrangiz Ebrahimi-Mameghani, E-mail: mebrahimimameghani@gmail.com

of high-sensitivity C-reactive protein (hs-CRP), a marker of systemic inflammation and a mediator of atherothrombotic disease, is in significant correlation with cardiovascular disease risk; inflammation is a major factor in atherothrombotic disease.[16] Global risk assessment uses hs-CRP as an index in the primary prevention of cardiovascular disease.[17]

Probiotics, live microorganisms providing a health benefit on their host when used in adequate amounts[18], are of beneficial effects in the prevention and treatment of different disease. Heterogeneous results have been given on the effects of probiotics consumption on the plasma lipid profile in different studies; yet, positive changes in lipid profile have been observed with the use of probiotics.[19,20] In addition, probiotics not only are of useful effects on cellular immunity but also help to preserve the balance between pro- and anti-inflammatory cytokines.[21] Despite the introduction of numerous pharmacologic lipid lowering therapies, there are known side effects.[22] Hence, the use of probiotics considering their natural and safe properties and low ability of triggering adverse effects[23] seems logical for serum lipid improvement.

The purpose of this randomized clinical trial was to determine the effect of probiotic containing lactobacillus, bifidobacterium and streptococcus thermophilus on lipid profile and hs-CRP levels in critically ill patients in the intensive care unit.

Methods

After approval of ethics committee of Tabriz University of Medical Sciences and obtaining written informed consent from the patients or their legal guardians, 40 patients who were admitted between December of 2011 and October of 2012 to the ICU of the Shohada Hospital (Tabriz, Iran) were enrolled in this trial. Inclusion criteria were critically ill patients who were expected to stay in ICU for at least 7 days aged 18 to 40 years old receiving enteral nutrition. Exclusion criteria were patients who could not tolerate enteral nutrition, those with unstable hemodynamic, immune disorders, history of diabetes mellitus and hyperlipidemia, intestinal obstruction or ischemia, cancer and patients who were expected to expire in the next 24 hours. Patients were randomized to two 20-person groups; the first group received standard treatment plus placebo and the second group received standard treatment plus VSL#3, 2 sachets daily for 7 days. Each sachet of probiotics (VSL#3; VSL Pharmaceuticals, Ft Lauderdale, FL) contained 450 billion viable lyophilized bacteria consisting of 4 strains of *Lactobacillus* (*L. casei*, *L. plantarum, L. acidophilus,* and *L. delbrueckii* subsp. *Bulgaricus)*, 3 *strains* of *Bifidobacterium* (*B. longum*, *B. breve,* and *B. infantis*) and *Streptococcus salivarius* subsp. *Thermophilus*.

All patients received enteral nutrition with Fresubin original fibre (*Fresenius Kabi, Homburg*, Germany) at the first 24-hour of admission via nasogastric tube. Energy requirements were calculated as 25–30 kcal/kg. Fasting blood samples were obtained from each patient to evaluate lipid profile and hs-CRP on days 1 and 7. Serum triglyceride, total cholesterol, and HDL-cholesterol concentrations were determined by routine clinical assays using commercial kits on an automated analyzer. Serum LDL-cholesterol concentrations were calculated based on the Friedewald calculation (LDL = TC - HDL - TG/5). Data were analyzed by SPSS 16.

P values<0.05 were considered significant for all statistical tests.

Results

There were 20 patients in each group. No significant differences in patients' demographic data between two groups were observed (Table 1). Levels of TG, total cholesterol, LDL-C, HDL-C and hs-CRP at the baseline and at the end of the study are shown in Table 2. There was a significant difference between two groups in levels of TG, HDL and hs-CRP at the end of the study (*P*= 0.043, <0.001 and 0.003, respectively); however, there was no significant difference in total cholesterol and LDL-C levels. In addition, levels of TG significantly decreased while levels of HDL-C significantly increased after the treatment period in probiotic group (*P*= 0.001 and 0.041, respectively).

Levels of hs-CRP in both groups are shown in Figure 1.

Table 1. Demographic data of patients

	Control group	Probiotic group	*P* value
Age (year)	35.60±5.03*	33.60±5.50	0.238
Male/Female	14/6	13/7	0.500
BMI	24.70±3	24.30±2.92	0.677

*mean±SD, BMI: Body Mass Index

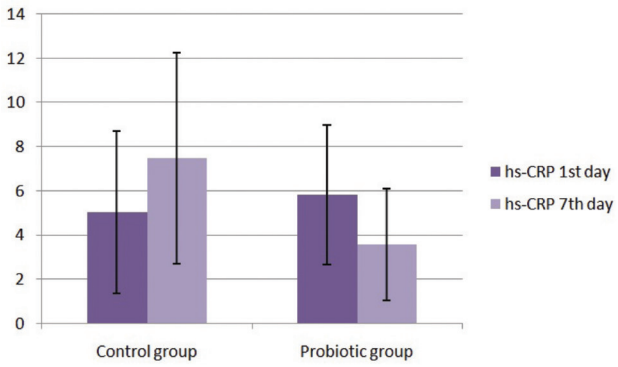

Figure 1. Mean (±SD) hs-CRP levels in two groups of patients.

Discussion

The present study used a double-blind, placebo-controlled, randomized design to determine the effects of probiotics on lipid profile and inflammation in critically ill, enterally

Table 2. Levels of lipid profile and hs-CRP at baseline and at the end of the study

		Control group	Probiotic group	*P* value
TG(mg/dl)	1st day	146.85±68.38*	178.70±57.98	0.120†
	7th day	171.70±89.97	126.70±34.07	**0.043**
Cholesterol(mg/dl)	1st day	129.85±30.00	150.65±47.88	0.108
	7th day	152.55±32.46	137.45±31.32	0.143
LDL(mg/dl)	1st day	61.48±26.47	76.79±44.10	0.191
	7th day	86.96±31.90	68.61±31.38	0.075
HDL(mg/dl)	1st day	39.00±14.29	38.00±11.63	0.810
	7th day	31.25±8.40	43.50±10.01	**<0.001**
hs-CRP(µg/ml)	1st day	5.02±3.69	5.82±3.16	0.471
	7th day	7.48±4.79	3.56±2.52	**0.003**

*mean±SD
†Independent-samples t-test

fed patients. A significant effect on the levels of TG and HDL-C was observed following adding probiotics to the enteral feeding of the patients; however, no significant effect was attained for total cholesterol and LDL-C in our study. In a study performed on 32 healthy subjects, it was reported that administration of probiotics was associated with a significant reduction in serum total cholesterol, LDL-C and TG and increase in HDL-C.[24] In another study on type 2 diabetic patients, no noteworthy changes were reported in TG and HDL-C, while probiotic group had significantly decreased total cholesterol levels: HDL-C ratio and LDL-C: HDL-C ratio.[25] In a meta-analysis, it was indicated that a probiotics rich diet decreases total cholesterol and LDL-C in participants with high, borderline high and normal cholesterol levels.[19] The varied effects of probiotics on lipid profile observed in the studies might be as a result of the type of the patient population and also the used probiotic. In our study, probiotics could not have applied their LDL-C lowering effects, as we assessed their effects in critically ill population who generally present Low LDL-C levels.[4]

The patients who received probiotic showed a significant reduction in hs-CRP levels. Hs-CRP as a marker of systemic inflammation is a strong independent predictor of risk of future myocardial infarction, stroke, peripheral arterial disease, and vascular death.[26-36] In the present study, a significant reduction in hs-CRP concentrations following the treatment course with probiotics was observed. Similar findings were reported by Asemi et al. who studied the effect of daily consumption of probiotic yoghurt vs. conventional yogurt on inflammatory factors in pregnant women. Their results showed that the probiotic yogurt decreased serum hs-CRP level, whereas there was no significant change in serum hs-CRP level in the conventional yogurt group.[37] In another study which compared a multifunctional (active) diet (AD) including a probiotic strain (Lactobacillus plantarum) with a control diet (CD) in healthy adults, CD did not alter the measured metabolic variables; however, AD changed hs-CRP levels significantly.[38] Yet, the results of this study cannot be credited to the sole probiotic; as a mixed multifunctional diet was used and the obtained results might have been due to the use of antioxidant-rich foods, oily fish or wholegrain products.

In conclusion, the results of this randomized trial suggest that administration of probiotics in critically ill patients compared to placebo-treated patients significantly reduces the levels of TG and hs-CRP and increases HDL-C levels. However, it does not significantly affect the levels of total cholesterol and LDL-C. Hence, further studies with larger sample sizes are required to clarify their usefulness in this group of patients.

Ethical issues: The study was approved by the institutional review board, and written informed consent was obtained from all participants.

Competing interests: The authors had no competing interests to declare in relation to this article.

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